

Application Serial No. 10/727,195

HUIP-P02-032

REMARKS

Claims 1, 3-4 and 25-35 are pending in the instant application.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Applicants have amended claims 27 and 29-31 to improve the clarity of the claims.

Claim 27 has been amended to clarify that the method, which comprises contacting lung cells provided in culture, uses lung cells which are not present in the culture as part of a tissue or organ (e.g., the lung cells are dispersed – rather than present in the culture as part of a tissue explant or organ culture). Support for Applicants' amendment can be found, for example, in paragraph [0039] of the published specification.

Claims 29-31 have been amended to clarify that the agent interacts with a protein other than patched. Support for Applicants' amendment can be found, for example, in paragraphs [0175] and [0182] of the published specification.

Support for Applicants' amendments are found throughout the specification and previously pending claims. No new matter has been entered.

Applicants add new claims 32-35. Support for the subject matter of the newly added claims is found throughout the specification. Specific support can be found, for example, in the abstract, claims 1, 3, 4, and 25, and in paragraphs [0010] and [0039] of the published specification. No new matter has been entered.

Status of Application, Amendments, and/or Claims

Applicants thank the Examiner for entering Applicants' July 7, 2008 amendment in full.

Information Disclosure Statement

Applicants thank the Examiner for consideration of the July 7, 2008 Information Disclosure Statement.

Withdrawn Objections and/or Rejections

Applicants thank the Examiner for the withdrawal of the rejection of claims 27 and 28 under 35 U.S.C. § 112, first paragraph.

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Rejection of Claims 1, 3, 4, 25, and 26 Under 35 U.S.C. § 103(a)

A. The Cited References Do Not Teach The Evaluation of Multiple Parameters

Claims 1, 3, 4, 25, and 26 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Marigo *et al.* (US 6,261,786) and Fujita *et al.* (BBRC 238: 658-665, 1997). Applicants respectfully traverse this rejection.

Applicants' July 7, 2008 Amendment detailed why the cited references fail to render the claimed invention obvious, and Applicants maintain the arguments advanced in the Amendment. In response to Applicants' arguments, the Examiner states that reliance on inherency is not included in the restated rejection. However, the Examiner continues to argue that the claimed method, which is directed to screening assays in which two parameters are evaluated, is obvious. The Examiner contends that while Marigo *et al.* and Fujita *et al.* teach different parameters for use in screening, the parameters are allegedly obvious when considered over Marigo *et al.* in view of Fujita *et al.* Applicants respectfully traverse.

The Examiner contends that Marigo *et al.* provides motivation for the obviousness of a method including evaluation of multiple parameters. Specifically, the Examiner points to the following statement in Marigo *et al.*, "the present invention facilitates the development of assays which can be used to screen for drugs, including hedgehog homologs, which are either agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides, or of their role in the pathogenesis of cellular differentiation and/or proliferation and disorders related thereto" (See column 48, lines 40-46). However, nowhere in Marigo *et al.*, or in Fujita *et al.*, is there any hint or suggestion to create a method that comprises determining, and evaluating relative to an appropriate control, both whether the agent inhibits or attenuates hedgehog signaling and whether the agent inhibits or reduces cell proliferation or growth. Indeed, the statement from Marigo *et al.* pointed to by the Examiner seems to imply that their screens are to be used for either identifying agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides or that these screens are to be used to determine the role of hedgehog agonists/antagonists in the pathogenesis of disease. There is no indication in either of the cited references, when considered alone or in combination, to utilize a combined approach in which multiple parameters are specifically evaluated, relative to a control.

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In view of the above arguments, Applicants contend that the combined teachings of Marigo *et al.* and Fujita *et al.* fail to undermine the patentability of the claimed invention. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

B. New Claims 32-35 Exclude Squamous Cell Cancer Cell Lines

The Examiner argues that the method of claims 1, 3, 25 and 26 is obvious over Marigo *et al.* in view of Fujita *et al.*. Specifically, the Examiner argues that Fujita *et al.* describes experiments involving lung cancer cells, and when viewed in combination with Marigo *et al.*, teaches the method of claims 1, 3, 25 and 26. For all of the reasons set forth above, Applicants disagree with the Examiner's argument. Applicants continue to contend that the method of claim 1, and therefore all of its dependent claims, are non-obvious over Marigo *et al.* and Fujita *et al.*. However, Applicants have added new claims 32-35, which recite a method that specifically excludes squamous cell cancer cell lines.

By excluding squamous cancer cell lines from claims 32-35, the obviousness rejection over Marigo *et al.*, in view of Fujita *et al.*, should be rendered moot. It was known at the time of the filing of the instant application that lung cancer cells could be categorized into two groups: Non-small cell lung cancer (NSCLC) cells and small cell lung cancer (SCLC) cells. NSCLC cells can be further categorized as adenocarcinoma cells and squamous cell carcinoma cells. Each of these cancer cell subgroups was known to be distinct from the other based on cell lineages, secretory properties and metastatic potential. Therefore, it would not have been considered obvious to one skilled in the art at the filing date to substitute one lung cancer cell type, *i.e.*, squamous cell carcinoma cells, with another lung cancer cell type, *i.e.*, adenocarcinoma cells or SCLC cells.

In view of the above arguments, Applicants contend that the combined teachings of Marigo *et al.* and Fujita *et al.* fail to undermine the patentability of the claimed invention set forth in claims 32-35.

Rejection of Claims 27 and 28 Under 35 U.S.C. § 103(a)

Claims 27 and 28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Marigo *et al.*, in view of Bellusci *et al.* (Development, 124:53-63, 1997), and further in view of Cardoso *et al.* (Developmental Dynamics, 207:47-59, 1996). Specifically, the Examiner contends that it would have been obvious to a person of ordinary skill in the art to prepare an embryonic

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lung cell culture by using the technique taught by Cardoso *et al.* and the Shh-overexpressing mice described by Bellusci *et al.* in order to perform hedgehog signaling screens as described in Marigo *et al.*. Applicants respectfully traverse.

The cultured lung cells of Cardoso were present in the form of lung explants from rats sacrificed at gestational day 13.5. As the Examiner has pointed to, these cultured lungs exhibit "airway branching and differentiation of both epithelium and mesenchyme, reproducing the overall proximal-to-distal pattern seen in lung in vivo" (page 49). Therefore, Cardoso is culturing large in tact pieces of lung tissue, and not dissociated lung cells in culture. Applicants have amended claim 27 to point out that the lung cells in culture used in the subject methods are not present in the culture as part of a tissue or organ (e.g., the lung cells are dispersed – rather than present in the culture as part of a tissue explant or organ culture). Support for Applicants' amendment can be found, for example, in paragraph [0039] of the published specification. Applicants submit that this amendment renders claim 27, and therefore dependent claim 28, non-obvious over the cited references.

In view of the above arguments, Applicants contend that the combined teachings of Marigo *et al.* and Bellusci *et al.* and Cardoso *et al.* fail to undermine the patentability of the claimed invention. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejection of Claims 29-31 Under 35 U.S.C. § 112, 1st Paragraph, Enablement

Claims 29-31 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not reasonably providing enablement for the method of claims 29-31, wherein the agent disrupts the association of patched with smoothened. Applicants respectfully disagree. However, in order to expedite prosecution, Applicants have amended claims 29-31 in order to improve their clarity.

Applicants have amended claims 29-31 so that they now recite a method of claim 1 (or 27 or 28), wherein the agent interacts with a protein other than patched. These claims therefore encompass agents that interact with any of the proteins downstream of patched that are still involved in the patched-mediated anti-proliferative signaling process. Examples of such proteins are listed in the specification and include the transcription factor cubitus interruptus (ci), the serine/threonine kinase fused (fu) and the gene products of costal-2, smoothened and suppressor of fused. See, e.g., paragraph [0182] of the published specification. This method limitation is

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defined and supported in the specification as filed, and therefore should not be considered new matter. See, e.g., paragraphs [0053] and [0175] of the published specification.

In view of the amendments to claims 29-31 and the above arguments, Applicants contend that amended claims 29-31 are fully enabled by the specification. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejection of Claims 29-31 Under 35 U.S.C. § 112, 2nd Paragraph

Claims 29-31 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner argues that it is unclear how the limitation recited in any one of claims 29-31 limits the agents of the parent claims. Applicants respectfully disagree. However, in order to expedite prosecution, Applicants have amended claims 29-31 in order to improve their clarity.

Applicants have amended claims 29-31, as described above. By focusing on proteins involved in patched-mediated signaling other than patched, claims 29-31 serve to appropriately limit the claims from which they depend.

In view of the amendments to claims 29-31 and the above arguments, Applicants contend that amended claims 29-31 are not indefinite. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Related Applications

The following co-pending applications were previously brought to the Examiner's attention and made of record in this case: application serial number 09/804,490; application serial number 09/977,864; application serial number 10/652,298; application serial number 09/883,848; application serial number 10/652,686; and application serial number 10/772,090. The Examiner is invited to consider all prior, ongoing, and future prosecution in these co-pending applications. Applicants note that application serial number 09/804,490 has issued as US Patent No. 7,445,778. US Patent No. 7,445,778 is made of record on the accompanying Information Disclosure Statement. Applicants note that application serial number 10/652,686 has been allowed and the issue fee has been paid.

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CONCLUSION

If any clarification of the above response would facilitate prosecution of this application, Applicants respectfully request that the Examiner contact the undersigned at 617-951-7000. Any fee required for timely consideration of this submission may be charged to **Deposit Account No. 18-1945, under Order No. HUIP-P02-032.**

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Respectfully Submitted,



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